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Title: Catalytic asymmetric synthesis of optically active a-halo-carbonyl compounds

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

18 February 2005

Susanne Morsing

PATENT- OG VAREMÆRKESTYRELSEN

Kongeriget Danmark

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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

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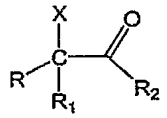
PATENT- OG VAREMÆRKESTYRELSEN

Background

The present invention is related to a process for the catalytic asymmetric synthesis of optically active α-halo-carbonyl compounds of the formula (1)



(1)

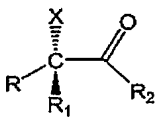
wherein R is an organic group; X is halogen; R_1 and R_2 which may be the same or different represents H, or an organic group, or R_1 and R_2 may be bridged together forming part of a ring system; R and R_2 may be bridged together forming part of a ring system; with the provisio that R and R_1 are different and R_2 when different from H is attached through a carbon-carbon bond.

An important goal for asymmetric catalysis is to develop new reactions affording optically active building blocks using simple and easily-available starting materials and catalysts. Optically active halogen containing compounds are especially attractive due to their high value as synthetic intermediates. Despite intensive research efforts over the past years, examples of highly enantioselective halogenation reactions are scarce and often limited to 1,3-dicarbonyl compounds or multi-step procedures requiring expensive reagents

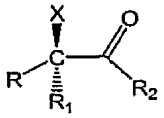
The compounds of general formula (1) are e.g. useful intermediates for the syntheses of pharmaceuticals such as antibiotics, agrochemicals, raw materials for chemicals and the like.

Description of the invention

In a first embodiment, the present invention provides a one-step catalytic asymmetric process for the synthesis of an optically active compound of formula (1a) or (1b)



(1a)

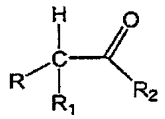


(1b)

wherein R is an organic group; X is halogen; R_1 and R_2 which may be the same or different

represents H or an organic group, or R_1 and R_2 may be bridged together forming part of a ring system; R and R_2 may be bridged together forming part of a ring system; with the provisio that R and R_1 are different and R_2 when different from H is attached through a carbon-carbon bond and,

comprising the step of reacting a compound of the formula (2)



(2)

with a halogenation agent and in the presence of a catalytic amount of a chiral nitrogen containing organic compound.

The compound represented by the general formula (1) is not limited to specified ones, as long as the object of the present invention is not hindered. In the general formula (1), R, R_1, R_2 includes, for instance, alkyl groups, alkenyl groups, alkynyl groups, haloalkyl groups, alkylaryl groups, aryl groups and heterocyclic groups, each of which may have one or more substituents.

For convenience, certain terms employed in the specification, examples and claims are collected here.

The term "catalytic amount" is recognised in the art and means a sub-stoichiometric amount relative to a reactant. As used herein, a catalytic amount means from 0.0001 to 90 mole percent relative to a reactant, preferably from 0.001 to 50 mole percent, and more preferably from 0.1 to 20 mole percent relative to a reactant.

The term "enantiomeric excess" (ee) is well known in the art and is defined for a resolution of the racemic mixture

ab → a + b as

$$ee_a = \left(\frac{\text{conc. of a - conc. of b}}{\text{conc. of a + conc. of b}} \right) \times 100$$

The value of ee will be a number between 0 and 100, zero being racemic and 100 being pure single enantiomer.

The term "alkyl" refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. Moreover, the term alkyl as used throughout the specification and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, a hydroxyl, a carbonyl, an alkoxyl, an ester, a phosphoryl, an amine, an amide, an imine, a silyl, a thiol, a thioether, a thioester, a sulfonyl, an amino, a nitro, an aryl, a heterocycle or an organometallic moiety. Representative examples of the alkyl group include groups having 1 to 20 carbon atoms in its hydrocarbon backbone, preferably 1 to 10 carbon atoms. When appropriate the number of carbon atoms designated in the hydrocarbon backbone for a substituent is assigned (i.e. C_{1-7} means one to seven carbons). It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term "alkenyl" refers to linear or branched groups of 2 to about 20 carbon atoms or, preferably, 2 to about 8 carbon atoms, having at least one carbon-carbon double bond. The term is intended to include both "unsubstituted alkenyls" and "substituted alkenyls" as described for alkyl above.

The term "alkynyl" refers to linear or branched groups of 2 to about 20 carbon atoms or, preferably, 2 to about 8 carbon atoms, having at least one carbon-carbon triple bond. The term is intended to include both "unsubstituted alkynyls" and "substituted alkynyls" as described for alkyl above.

The term "haloalkyl" refers to an alkyl group, as defined above, wherein one or more

hydrogen atoms are replaced by a halogen atom.

The term "aryl" refers to a carbocyclic aromatic system containing one or more rings wherein such rings may be attached together in a pendent manner or may be fused. Examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogens, alkyls, alkenyls, alkynyls, hydroxyl, amino, nitro, thiol, amines, imines, amides, carbonyls, carboxyls, ethers, thioethers, sulfonyls, ketones, aldehydes, esters or the like.

The term "alkylaryl" refers to aryl-substituted alkyl groups. Preferable alkylaryl groups are "lower alkylaryl" groups having aryl groups attached to alkyl groups having 1 to 6 carbon atoms. Even more preferred lower alkylaryl groups are phenyl attached to alkyl portions having 1 to 3 carbon atoms. Examples of such groups include benzyl, diphenylmethyl and phenylethyl. The aryl in said alkylaryl may be additionally substituted as defined above. When appropriate the number of carbon atoms designated in the hydrocarbon backbone of the alkyl part is assigned (i.e. C_{1-3} alkylaryl means an alkylaryl group where the alkyl part contains one to three carbon atoms).

The term "heterocyclic" refers to 3 to 10-membered ring structures, which include at least one heteroatom preferably selected from O, S or N, and which may be aromatic (heteroaryl). Examples of such structures include pyridine, pyrimidine, piperidine, triazole, thiophene, furane, morpholine, chromane, indole, oxazole etc. The heterocycle may be substituted in one or more ring positions as mentioned for the aryl groups.

The term "amino" refers to a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an alkyl or phenyl substituent and the tertiary amino group carrying two similar or different substituents or the two nitrogen substituents together forming a ring. The substituents may be additionally substituted as defined above, and as such the amino group may form part of an amino acid moiety.

When two substituents are bridged together, they are joined through a bridging group, e.g via

an alkylene, alkenylene, or alkynylene radical chain optionally with one or more of the carbon atoms substituted with a heteroatom, said chain optionally being substituted with one or more substituents.

The term "halogen" designates F, Cl, Br or I.

When any variable may occur more than one time in any formula for a compound, its definition on each occurrence is independent of its definition at every other occurrence.

R is preferably an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{2-8} alkylene group or a C_{1-3}-alkylaryl group. More preferably R is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-4} alkylene group or a C_{1-2}-alkylaryl group.

R_1 is preferably H or an optionally substituted C_{1-10} alkyl group. More preferably R_1 is H or an optionally substituted C_{1-4} alkyl group.

R_2 is preferably H or an optionally substituted C_{1-10} alkyl group or R and R_2 are bridged together forming part of a ring system. More preferably R_2 is H or together with R forms an optionally substituted C_{3-5}-alkylene bridge.

X is preferably Cl or Br and more preferably Cl.

In a preferred embodiment of the present invention R_1 and R_2 both represents H and R represents an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-4} alkylene group or a C_{1-2}-alkylaryl group. More preferably R is attached through a $-CH_2-$ group.

In another preferred embodiment of the present invention R_1 is H and R and R_2 each represents an optionally substituted C_{1-10} alkyl group or R_2 together with R forms an optionally substituted C_{3-5}-alkylene bridge optionally with one or more of the carbon atoms being replaced by a heteroatom.

In principle any solvent that is capable of dissolving the reagents and the catalysts in suitable

amounts and which is inert with respect of the reaction may be used. The solvent employed in the reaction may be either protic, aprotic, mixtures of both or ionic liquids. Suitable protic solvents include, water, alcohols e.g. straight, branched or cyclic alkanols and halogenated alkanols, aromatic alcohols; amines and organic acids. Suitable aprotic solvents include dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), N-methylpyrrolidone, dimethylsulfoxide (DMSO), pyridine, alkanes and haloalkanes, ethers, ketones, aldehydes, nitriles, and nitroalkanes. The compound of formula (2) may also serve the purpose of solvent when in its liquid state at the reaction temperature.

Examples of halogenation agents are: N-halogenated amides such as, N-halosuccinimides e.g. N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide, N-halophthalimide e.g. N-chlorophthalimide, N,N'-dihalodimethylhydantoin e.g. N,N'-dichlorodimethylhydantoin, N-halosaccharine e.g. N-chlorosaccharine or N-bromosaccharine, 1,3,5-trihalo-1,3,5-triazine-2,4,6-trione e.g. 1,3,5-trichloro-1,3,5-triazine-2,4,6-trione, N-haloglutarimide e.g. N-chloroglutarimide, N-chloro-N-cyclohexyl-benzenesulfonimide; interhalogen compounds such as ICl or IBr; SO_2X_2 e.g. SO_2Cl_2; $(Ph)_3PX_2$ e.g. $(Ph)_3PCl_2$ or $(Ph)_3PBr_2$; $(Ph)_3/CX_4$ e.g. $[(Ph)_3CCl_3]Cl$; complexed halogens such as pyridin-HBr-Br_2 or $(CH_3)_2S$-Br_2; t-BuOCl; elemental halogen e.g. Cl_2 or Br_2; 2,3,4,5,6,6-Hexachloro-2,4-cyclohexadien-1-one and 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one.

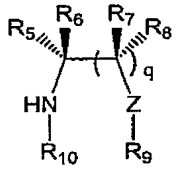
A preferred halogenation agent is N-chlorosuccinimide (NCS).

The amount of halogenation agent relative to the compound (2) depends on the amount of 'active' haloatoms on the halogenation agent, but in case of one active haloatom as in N-halosuccinimide, the amount is usually 1-4 equivalents, preferably 1-2.5.

It has further been found that addition of acids to the reaction media has a positive effect on the reaction rate and yield of the compound (1). Preferably the acid(s) is selected among carboxylic acids such as aliphatic and aromatic carboxylic acids. Examples of such acids are acetic acid, trifluoroacetic acid, chloroacetic acid, benzoic acid and nitro substituted benzoic acids e.g. 2-nitrobenzoic acid. The amount of acid relative to the compound (2) is 0-200 mole percent, preferably 0-60 mole percent.

Any chiral nitrogen containing organic compound capable of inducing asymmetric halogenation can be used as catalyst. Preferred are catalysts having a primary or secondary nitrogen atom.

Examples of the chiral nitrogen containing organic compound used as catalyst include, but are not limited to, the following compound (3):



(3)

wherein q is 0 or 1;

R_5, R_6, R_7, R_8, which may be the same or different represents H, alkyl, haloalkyl, COR_{11}, optionally substituted aryl, an optionally substituted heterocycle, alkyl substituted with at least one OH group, an optionally substituted amino group or optionally substituted aryl or heterocycle or R_5 and R_6 together or R_7 and R_8 together may represent a carbonyl group or when q is 1, R_5 with either R_7 or R_8 may be bridged together forming part of a ring system;

R_{11} represents an optionally substituted amino group or OR_{12} wherein R_{12} represents H, alkyl or phenyl;

R_9 and R_{10}, which may the same or different represents H, alkyl, OH, alkoxy or R_9 and R_{10} may be bridged together forming part of a ring system;

Z is S, O, C=O, CH-R_{14}, N-R_{14} wherein R_{14} is R_5;

In a preferred embodiment of the present invention, q is 1; R_5, R_6, R_7, R_8 which may be the same or different represents H, COR_{11}, optionally substituted aryl preferably phenyl or benzyl, or methyl substituted with at least one of the following, an OH group, an optionally substituted amino group or an optionally substituted aryl or heterocycle group; or R_5 and R_7 together represents a C_{3-5} alkylene bridge;

R_{11} represents OH, NH_2 or NH-alkyl;

R_9 and R_{10} are H or R_9 and R_{10} together represents a methylene bridge optionally substituted with phenyl, benzyl, COOH or CO– alkoxy;

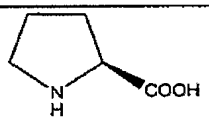
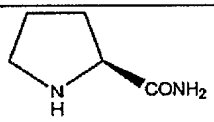
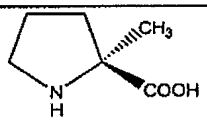
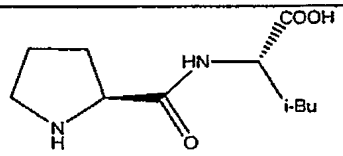
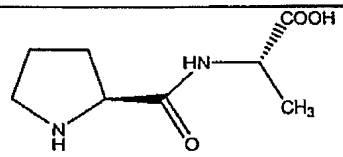
Z is CH-R_{14} or N-R_{14} wherein R_{14} represents H or alkyl;

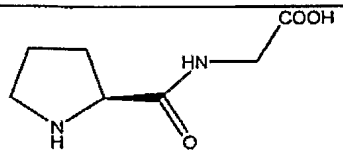
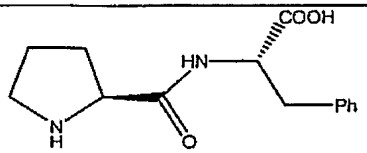
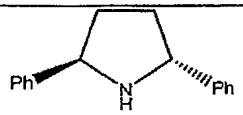
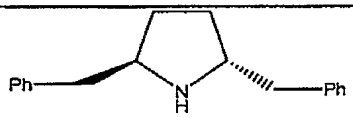
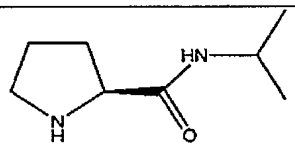
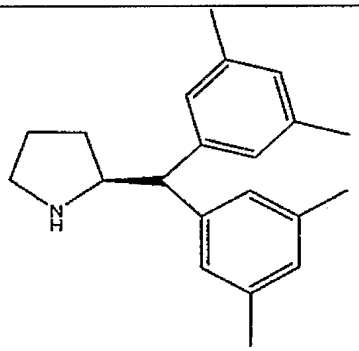
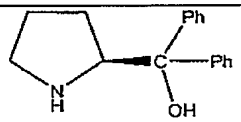
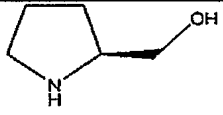
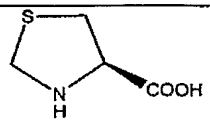
In a more preferred embodiment the substituent pair (R_5/R_6) is identical to the pair (R_7/R_8).

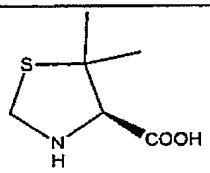
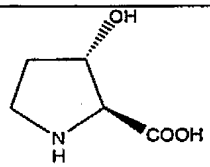
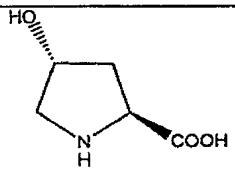
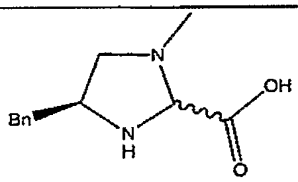
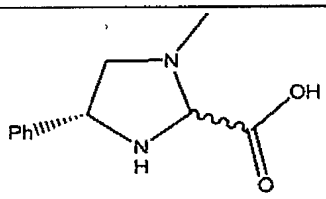
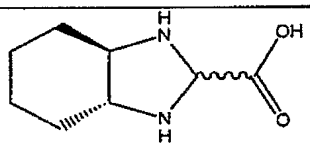
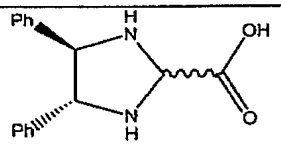
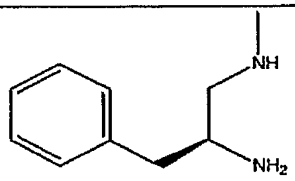
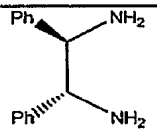
In an even more preferred embodiment either R_5 or R_6 represents H; R_7 and R_8 represents H; R_9 and R_{10} together represents a methylene bridge and Z is CH_2.

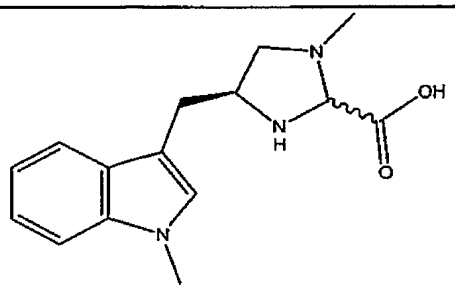
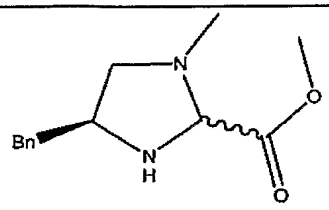
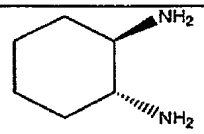
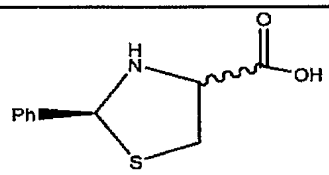
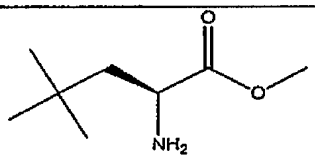
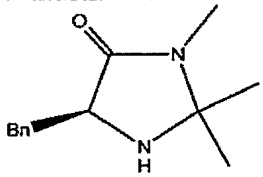
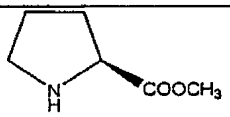
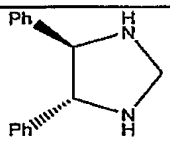
The chiral nitrogen containing organic compound used as catalyst may be chosen among the compounds shown in Table 1, where the stereoconfiguration shown merely serves an illustrative purpose:

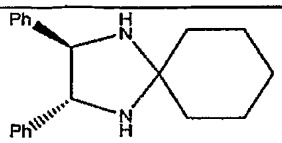
Table 1

Structure	Name
	L-proline
	L-prolinamide
	2-methyl-L-proline
	L-prolyl-L-leucine
	L-prolyl-L-alanine

	L-prolylglycine
	L-prolyl-L-phenylalanine
	(2*R*,5*R*)-diphenylpyrrolidine
	(2*R*,5*R*)-dibenzylpyrrolidine
	N-(1-methylethyl)-(2*S*)-pyrrolidinecarboxamide
	(2*S*)-(anilinomethyl)pyrrolidine
	(2*S*)-[bis(3,5-dimethylphenyl)methyl]-pyrrolidine
	diphenyl((S)-pyrrolidin-2-yl)methanol
	L-prolinol
	(4*S*)-thiazolidinecarboxylic acid

	5,5-dimethyl-(4*S*)-thiazolidinecarboxylic acid
	*trans*-3-hydroxy-L-proline
	*trans*-4-hydroxy-L-proline
	(4*S*)-benzyl-1-methyl-imidazolidine-2-carboxylic acid
	1-methyl-(4*R*)-phenyl-imidazolidine-2-carboxylic acid
	(4*R*,5*R*)-octahydro-benzoimidazole-2-carboxylic acid
	(4*S*,5*S*)-diphenyl-imidazolidine-2-carboxylic acid
	(*S*)-N^1-methyl-3-phenyl-propane-1,2-diamine
	(1*R*,2*R*)-diphenylethanediamine

	1-methyl-(4*S*)-(1-methyl-1H-indol-3-ylmethyl)-imidazolidine-2-carboxylic acid
	(4*S*)-benzyl-1-methyl-imidazolidine-2-carboxylic acid methyl ester
	(1*R*,2*R*)-cyclohexanediamine
	(2*S*)-phenyl-thiazolidine-4-carboxylic acid
	(*S*)-*tert*-leucine methyl ester
	(5*S*)-benzyl-2,2,3-trimethyl-imidazolidin-4-one
	L-methyl prolinate
	(*R*,*R*)-4,5-diphenylimidazolidine

	(*R*,*R*)-2-cyclohexyl-4,5-diphenylimidazolidine

The selection of the stereochemistry of the catalyst depends on the stereochemistry of the desired compound and by proper choice of catalyst one can prepare compounds of either formula (1a) or (1b) as illustrated in the examples. The catalyst can be bound to a support or be unsupported.

The amount of catalyst may be as high as 90 mole percent relative to the compound (2). In principle there is no lower limit to the amount of catalyst employed, however, in practice the desire of a suitable high reaction rate dictates a certain lower limit. The catalyst may conveniently be separated from the final reaction mixture and reused in subsequent reactions according to the present invention.

The reaction may conveniently be carried out at temperatures between –90°C and 100°C, preferably between -30°C to 50°C.

No displacement of any other substituents with halogen other than the alfa-hydrogen atom on the compound (2) is observed in the reaction according to the present invention.

The starting compound (2), and the chiral nitrogen containing organic compounds used as catalysts are commercially available or can be synthesised according to known methods.

The invention is illustrated by the following non-limiting examples:

Example 1 – preparation of (*R*)–2-chloro-3-methylbutanal

0.57 g (5.0 mmol) of (L)-prolinamide is added to a stirred solution of 5.4 ml (50 mmol) of 3-methylbutanal in 65 ml of methylene chloride cooled to 0°C in an ice bath. 8.7 g (65 mmol) of N-chlorosuccinimide is then added, the ice bath removed and the mixture allowed to warm to 20°C. Stirring is continued until the aldehyde is consumed as shown by ^{1}H-NMR and gas chromatography of the mixture after 1-2 hours. 200 ml of pentane is then added, and the

precipitated solids filtered off. The solvent is then evaporated, and 50 ml of pentane added to the residue. After filtration and evaporation of the pentane (R)-2-chloro-3-methylbutanal was obtained. Yield 5.1g (85% of theory). The compound is identical to an authentic racemic sample on non-chiral gas chromatography and ^{1}H-NMR. The ee is determined to be 80% by gas chromatography on a Chrompack CP-Chirasil Dex CB-column, and the absolute configuration determined as (R) by reduction to 2-chloro-3-methyl-butan-1-ol with sodium borohydride in methanol and comparison of the optical rotation of this product with the literature value. (Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, page 317)

Example 2
Using the procedure as in Example 1, the following 2-chlorocarbonyls were obtained:

Table 2

Compounds of the formula (1a) or (1b) wherein X is Cl.

R	R_2	R_1	Catalyst	Yield (%)	Ee (%)
Ethyl	H	H	L-prolinamide	99	80(*R*)
Methyl	H	H	- " -	99	75(*R*)
iso-Propyl	- " -	- " -	- " -	>90	87(*R*)
n-Hexyl	- " -	- " -	- " -	95	70(*R*)
Allyl	- " -	- " -	- " -	>90	74(nd)
Benzyl	- " -	- " -	- " -	75	78(nd)
Phenyl	H	CH_3	- " -	20	16(nd)
$-(CH_2)_4-$		H	- " -	30	76(nd)
Ethyl	H	H	(2*R*,5*R*)-diphenyl pyrrolidine	>90	95(*S*)
Methyl	- " -	- " -	- " -	99	31(nd)
iso-Propyl	- " -	- " -	- " -	>90	94(*S*)
tert-Butyl	- " -	- " -	- " -	30	95(nd)
n-Hexyl	- " -	- " -	- " -	99	95(*S*)
Allyl	- " -	- " -	- " -	>90	95(nd)

Benzyl	- " -	- " -	- " -	82	95(nd)

nd = absolute configuration not determined

Example 3 – preparation of (*R*)-2-chloro-3,3-dimethylbutanal

5.7 mg (0.05 mmol) of (L)-prolinamide is added to a stirred solution of 50 mg (0.5 mmol) of 3,3-dimethylbutanal in 1 ml of methylene chloride cooled to -78°C in a dry ice bath. 87 mg (0.65 mmol) of N-chlorosuccinimide is then added, and the mixture is warmed to -24°C. Stirring is continued at –24°C until the aldehyde is consumed as shown by ^{1}H-NMR and gas chromatography of the mixture (approx. 12 h). The yield of (*R*)–2-chloro-3,3-dimethylbutanal is determined by gas chromatography to be >90% of theory. The ee is determined to be 95% by gas chromatography on a Chrompack CP-Chirasil Dex CB-column, and the absolute configuration determined as (R) by X-ray crystallography after reduction to (2*R*)-chloro-3,3-dimethylbutan-1-ol with sodium borohydride.

Example 4 – preparation of 2-chloro-4-(*tert*-butyldimethylsilyloxy)-butanal

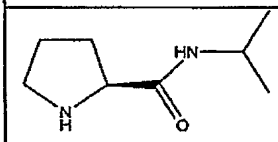
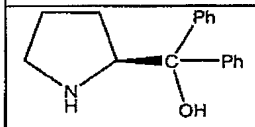
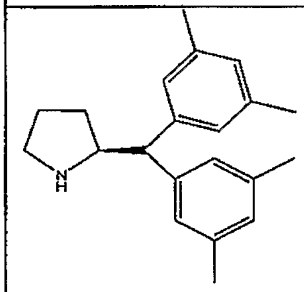
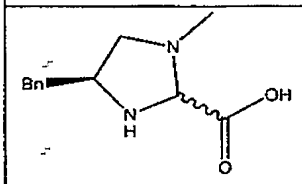
By the procedure in Example 3, employing 0.10 ml (0.50 mmol) of 4-(*tert*-butyldimethylsilyloxy)-butanal, (2*R*)-chloro-4-(*tert*-butyldimethylsilyloxy)-butanal was obtained. Yield 95% of theory, ee 81%, absolute configuration not determined.

Example 5 - preparation of enantiomers of 2-chloro-3-methylbutanal

Using the procedure as in Example 1 with 3-methylbutanal, the following results using various catalysts and 1.3 equivalents of N-chlorosuccinimide were obtained:

Table 3

Catalyst	Catalyst mol%	Reaction time (Hour)	Solvent	Yield (%)	Ee (%)
L-proline	20	1	$CHCl_3$	>95	23(*R*)
- " -	20	1	CH_2Cl_2	>95	25(*R*)
2-methyl-L-proline	20	5	DCE	76	60(*R*)
L-prolineamide	20	3	DCE	>95	78(*R*)
- " -	20	1	Ethanol	<5	28(*R*)
- " -	20	1	THF	23	30(*R*)

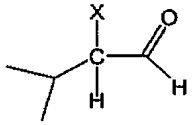
- " -	10	1	CH_2Cl_2	>95	82(*R*)
	20	0.5	DCE	>95	54(*R*)
L-prolylglycine	20	1	DCE	33	81(R)
L-prolinol	20	1	DCE	34	77(*R*)
	20	1	DCE	15	85(*R*)
	20	0.5	DCE	92	64(*S*)
(2*R*,5*R*)-diphenylpyrrolidine	20	0.5	DCE	>95	94(*S*)
- " -	10	1	DCE	>95	94(*S*)
- " -	5	1	DCE	77	94(*S*)
(2*R*,5*R*)-dibenzylpyrrolidine	20	1	DCE	<10	78(*R*)
L-prolyl-L-leucine	20	1	DCE	39	57(*R*)
L-prolyl-L-phenylalanine	20	1	DCE	31	59(*R*)
L-prolyl-L-alanine	20	1	DCE	21	61(*R*)
	20	1	DCE	52	23(*S*)
(1*R*,2*R*)-cyclohexanediamine	10	18	CH_2Cl_2	18	15(*R*)
(1*R*,2*R*)-diphenylethanediamine	10	18	CH_2Cl_2	16	73(*R*)

DCE = 1,2-Dichloroethane, THF = Tetrahydrofuran.

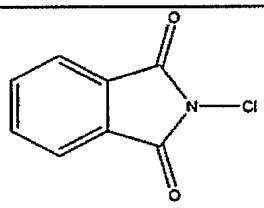
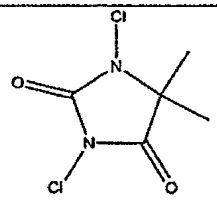
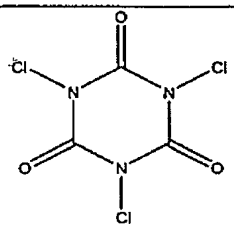
Example 6

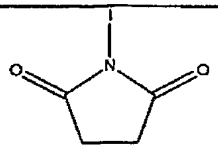
Using the procedure as in Example 1 with 3-methyl butanal, the following results using various halogenation reagents and 20 mol% of various catalysts:

Table 4, compounds of the formula (1')



(1')

Halogenation agent	Equivalents relative to compound (2)	Catalyst	Solvent	Yield (%)	Ee (%)
 X=Cl	2.0	L-prolinamide	DCE	17	76(*R*)
- " -	2.0	(2*R*,5*R*)-diphenylpyrrolidine	DCE	26	93(*S*)
 X=Cl	1.3	(2*R*,5*R*)-diphenylpyrrolidine	CH_2Cl_2	12	76(*S*)
 X=Cl	1.0	L-prolinamide	CH_2Cl_2	20	61(R)

 X=I	2.0	(2*R*,5*R*)-diphenylpyrrolidine	DCE	100	24(nd)
- " -	2.0	L-prolinamide	DCE	22	13(nd)

DCE = 1,2-Dichloroethane

nd = absolute configuration not determined

Example 7 – preparation of 2-bromo-3,3-dimethylbutanal

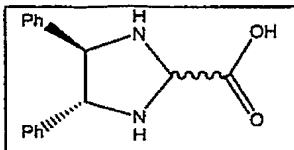
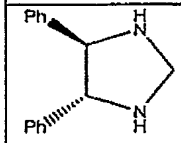
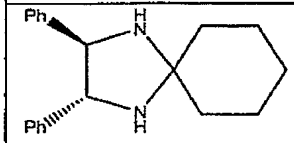
11.1 mg (0.05 mmol) of (2*R*,5*R*)-diphenylpyrrolidine is added to a stirred solution of 50 mg (0.5 mmol) of 3,3-dimethylbutanal in 1 ml of methylene chloride cooled to -78°C in a dry ice bath. 115.7 mg (0.65 mmol) of N-bromosuccinimide is then added, and the mixture is warmed to -24°C. Stirring is continued at –24°C until the aldehyde is consumed as shown by ^{1}H-NMR and gas chromatography of the mixture (approx. 2 h). The yield of 2-bromo-3,3-dimethylbutanal is determined by gas chromatography to be ca. 10% of theory. The ee is determined to be 80% by gas chromatography on a Chrompack CP-Chirasil Dex CB-column, absolute configuration not determined.

Example 8 – preparation of 2-chlorocyclohexanone

A series of experiments were performed to prepare optically active 2-chlorocyclohexanone from cyclohexanone in the presence of various catalysts using the following procedure: To a mixture of cyclohexanone and catalyst in CH_2Cl_2 was added N-chlorosuccinimide (0.5 mmol) and the reaction mixture stirred at ambient temperature for the time indicated in Table 5. Ee was determined CSP-GC and the yield determined by GC.

Table 5

Catalyst	Cyclohexanone (mmol)	Catalyst mol%	Reaction time (Hour)	Yield (%)	Ee (%)
L-prolinamide	2.5	20	24*	40	81(R)
L-methyl prolinate	2.5	20	24	20	20(R)

	2.5	20	0.75	10	62(R)
	2.5	20	20**	88	95(R)
	2.5	20	22	17	88(R)

* Reaction performed at -24°C. ** Reaction performed at -10°C.

Example 9 – influence of addition of organic acids

A series of experiments were performed to prepare optically active 3-chlorotetrahydropyran-4-one from tetrahydropyran-4-one, in various solvents using (*R*,*R*)-4,5-diphenylimidazolidine as catalyst and in the presence of an organic acid, by the following procedure: To a mixture of tetrahydropyran-4-one, organic acid, solvent (1 mL), and the catalyst (0.05 mmol), was added N-chlorosuccinimide (NCS) and the reaction mixture stirred at -10°C for a period of 24 hours. Ee was determined CSP-GC and the yield determined by GC.

Table 6

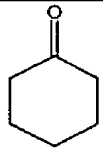
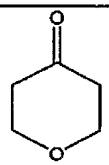
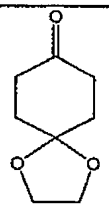
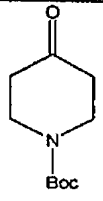
Tetrahydro-pyran-4-one (mmol)	Acid (Equiv.)	Solvent	NCS (Equiv.)	Yield (%)	Ee (%)
5	-	CH_2Cl_2	1	30	30
5	$PhCO_2H$	CH_2Cl_2	1	53	84
2.5	$PhCO_2H$	MeCN	1	15	97
2.5	AcOH	MeCN	1	19	87
5*	CF_3CO_2H	CH_2Cl_2	1	62	68
2.5	$ClCH_2CO_2H$	MeCN	1	50	91
1	2-NO_2-$PhCO_2H$	MeCN	1.5	63	97
1	2-NO_2-$PhCO_2H$	MeCN	2.0	72	98

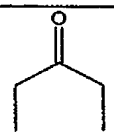
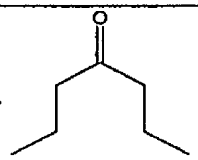
Example 9 – preparation of α-halo cyclic and acyclic ketones

A series of experiments were performed to prepare optically active α-halo cyclic and acyclic ketones from the corresponding ketone using the following general procedure: To mixture of ketone, (*R*,*R*)-4,5-diphenylimidazolidine as catalyst and 2-NO_2-$PhCO_2H$ in MeCN was added N-chlorosuccinimide (1.0 mmol) and the reaction stirred for a period of 20 hours.

Ee was determined CSP-GC and the yield determined by ^1H NMR using an internal standard and confirmed using GC analysis.

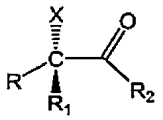
Table 7

Ketone (mmol)	2-NO_2-$PhCO_2H$ (mmol)	Catalyst (mmol)	Reaction temp (°C)	Yield (%)	Ee (%)
 (0.5)	0.25	0.1	-24	82	97
 (0.5)	0.125	0.05	-24	72	98
 (0.5)	0.25	0.1	-24	83	90
	0.25	0.1	-24	76	93

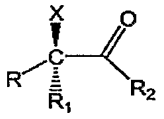
(0.5)					
 (2.5)	0.25	0.1	-10	62	83
 (2.5)	0.25	0.1	-10	40	88

Claims

1. A process for the catalytic asymmetric synthesis of an optically active compound of the formula (1a) or (1b)



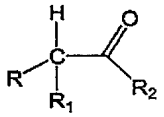
(1a)



(1b)

wherein R is an organic group; X is halogen; R_1 and R_2 which may be the same or different represents H, or an organic group or R_1 and R_2 may be bridged together forming part of a ring system; R and R_2 may be bridged together forming part of a ring system; with the provisio that R and R_1 are different and R_2 when different from H is attached through a carbon-carbon bond,

comprising the step of reacting a compound of the formula (2)



(2)

with a halogenation agent in the presence of a catalytic amount of a chiral nitrogen containing organic compound.

2. The process according to claim 1 wherein R_2 is H or an optionally substituted C_{1-10} alkyl group or R and R_2 are bridged together forming part of a ring system.

3. The process according to claim 1 or 2 wherein R_1 is H or an optionally substituted C_{1-10} alkyl group.

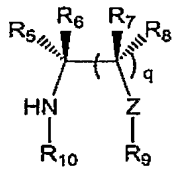
4. The process according to any of the preceding claims wherein R is an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{2-8} alkylene group or a C_{1-3}-alkylaryl group.

5. The process according to claim 4 wherein R is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-4} alkylene group or a C_{1-2}-alkylaryl group.

6. The process according to claim 4 or 5 wherein R_1 and R_2 are H.

7. The process according to claim 1 wherein the chiral nitrogen containing organic compound is selected among compounds having a primary or secondary nitrogen atom.

8. The process according to claim 7 wherein the chiral nitrogen containing organic compound is selected among compounds of the formula (3)



(3)

wherein q is 0 or 1;

R_5, R_6, R_7, R_8, which may be the same or different represents H, alkyl, haloalkyl, COR_{11}, optionally substituted aryl, an optionally substituted heterocycle, alkyl substituted with at least one OH group, an optionally substituted amino group or optionally substituted aryl or heterocycle or R_5 and R_6 together or R_7 and R_8 together may represent a carbonyl group or when q is 1, R_5 with either R_7 or R_8 may be bridged together forming part of a ring system;

R_{11} represents an optionally substituted amino group or OR_{12} wherein R_{12} represents H, alkyl or phenyl;

R_9 and R_{10}, which may the same or different represents H, alkyl, OH, or alkoxy; or R_9 and R_{10} may be bridged together forming part of a ring system;

Z is S, O, C=O, CH-R_{14}, N-R_{14} wherein R_{14} is R_5;

9. The process according to claim 8 wherein q is 1; R_5, R_6, R_7, R_8 which may the same or different represents H, COR_{11}, optionally substituted aryl or methyl substituted with at least one of the following; an OH group, an optionally substituted amino group or an optionally substituted aryl or heterocycle group; or R_5 and R_7 together represents a C_{3-5} alkylene bridge;

R_{11} represents OH, NH_2 or NH-alkyl;

R_9 and R_{10} are H or R_9 and R_{10} together represents a methylene bridge optionally

substituted with phenyl, benzyl, COOH or CO–alkoxy;
Z is CH-R_{14} or N-R_{14} wherein R_{14} represents H or alkyl;

10. The process according to claim 9 wherein either R_5 or R_6 represents H; R_7 and R_8 represents H; R_9 and R_{10} together represents a methylene bridge and Z is CH_2.

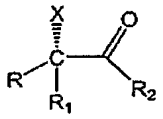
11. The process according to claim 3 wherein R_1 is H and R and R_2 each represents an optionally substituted C_{1-10} alkyl group or R_2 together with R forms an optionally substituted C_{3-5}-alkylene bridge optionally with one or more of the carbon atoms being replaced by a heteroatom.

12. The process according to claim 1 wherein one or more acids are added to the reaction media.

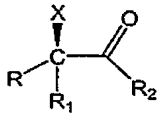
Catalytic asymmetric synthesis of optically active α-halo-carbonyl compounds

A B S T R A C T

A process for the catalytic asymmetric synthesis of an optically active compound of the formula (1a) or (1b)



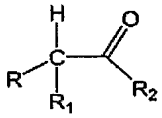
(1a)



(1b)

wherein R is an organic group; X is halogen; R_1 and R_2 which may the same or different represents H, or an organic group or R_1 and R_2 may be bridged together forming part of a ring system; R and R_2 may be bridged together forming part of a ring system; with the provisio that R and R_1 are different and R_2, when different from H, is attached though a carbon-carbon bond,

comprising the step of reacting a compound of the formula (2)



(2)

with a halogenation agent in the presence of a catalytic amount of a chiral nitrogen containing organic compound.